Are we ready to demystify age in glioblastoma? Or does older age matter in glioblastoma?

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Are we ready to demystify age in glioblastoma?

The strong negative impact on outcome of higher age in glioma patients has been noted ever since larger populations of glioma patients have been analyzed. However, the cut-off for defining "elderly" has remained controversial, and there is now little doubt that higher age is a surrogate marker for a changing biology of gliomas with age. In fact, it has often been (inofficially) speculated (at conferences) that advanced neuro-oncologists simply define "elderly" as their own age plus 15. Undoubtedly, we must and can do better.

In this issue of *Neuro-Oncology*, Scott and colleagues (1) report a retrospective analysis of outcome by treatment administered in 206 patients with glioblastoma aged 70 or more diagnosed between May 1979 and September 2007. These patients had a median age of 75 years and a median overall survival of 4.5 months. Multivariate analysis confirmed higher Karnofsky score, surgery beyond biopsy, radiotherapy, and chemotherapy to be associated with longer survival. Although this analysis thus spans almost three decades of development in Neuro-Oncology, there is apparently a consistent trend for less aggressive treatment in the elderly, and (over)treated patients lived longer than (under)treated patients.

Altogether, Neuro-Oncology should be moving to concepts that characterize and understand age as a surrogate marker of a specific biological character of disease rather than the proximate course of poor outcome *per se*. The first step was the delineation and segregation of glio(blasto)mas carrying isocitrate dehydrogenase (IDH) mutations. Across all glioma entities, IDH-mutant tumors show a more favourable outcome. There are almost no patients with IDH-mutant anaplastic astrocytomas and glioblastomas above the age of 60. Accordingly, the differential distribution of IDH mutations may account for some of the apparent unfavourable prognostic impact of age hitherto attributed to age *per se* (2). A next

step may be resolving the apparent discrepancy between the high rate of O^6-methylguanylmethyltransferase (MGMT) promoter hypermethylation (3) and the still generally poor(er) outcome in the elderly.

Undoubtedly, the analysis of Scott and colleagues (1) justifies to explore the role of more aggressive approaches of treatment in elder glioblastoma patients. However, as long as we continue to compare the effects of aggressive treatment in good prognosis patients with the effects of less aggressive treatment in poor prognosis patients, we will not be able to justify a change in the standards of care. In this regard, it is important to note that the benefit derived from concomitant and adjuvant temozolomide decreases with increasing age (4). Whether this reflects lower activity or poorer tolerance of combined modality treatment, has remained controversial.

Fortunately, Neuro-Oncology is now rapidly moving to a definition of standards of care for older patients with glioblastoma based on data from randomized trials. The superiority of radiotherapy over best supportive is no longer disputed (5). Radiotherapy alone has been challenged by temozolomide chemotherapy alone both in the Nordic trial (6) and the NOA-08 trial (7). While temozolomide was equieffective to radiotherapy in the Nordic trial, but not in NOA-08, it is still conceivable that these apparent differences dissolve upon the analysis of survival by molecular markers and first-line and salvage treatment administered in these studies. Meanwhile, the NCIC EORTC trial, which compares hypofractionated radiotherapy alone versus hypofractionated radiotherapy plus concomitant and adjuvant temozolomide chemotherapy, takes the next step and is well under way

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